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EXAMINER	
KASSA, TIGABU	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,604	HOLMES ET AL.	
	Examiner	Art Unit	
	TIGABU KASSA	1619	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed January 28, 2010. **Claims 1-11 are currently pending. Claims 1-11 are under consideration in the instant office action.**

Maintained rejections

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness

Claims 1 and 3-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sorensen et al. (WO 00/74489) in view of Komer (US Patent No. 5773422).

Applicant Claims

Instant claim 1 recites a stable formulation suitable for administration to animals consisting essentially of a combination of levamisole and an avermectin or levamisole and a milbemycin dissolved in a pyrrolidone solvent. Instant claim 3 recites the stable formulation according to claims 1 or 2, wherein the pyrrolidone solvent is 2-pyrrolidone or N-methyl pyrrolidone. Instant claim 4 recites the stable formulation according to claims 1 or 2, wherein the avermectin or milbemycin is present in the range of between 0.01-5% w/v. Instant claim 5 recites the stable formulation according to claim 4, wherein the avermectin or milbemycin is selected from the group consisting of abamectin, doramectin, eprinomectin, ivermectin, and moxidectin. Instant claim 6 recites the stable formulation of according to claims 1 or 2, wherein the levamisole is present in the range of between 1-30% w/v. Instant claim 7 recites a stable formulation suitable for administering to animals consisting essentially of a combination of levamisole and an avermectin or levamisole and a milbemycin dissolved in a pyrrolidone solvent and at least one excipient selected from the group consisting of dietary supplements, vitamins, mineral, preservatives, stabilizers, flavorants, and co-solvents. Instant claims 8-10 recite the stable formulation suitable for administration to animals as claimed in claims 1 or 2, wherein the formulation is suitable for topical, parenteral, and oral administration, respectively.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Sorensen et al. teach a stable biocidal composition (title) comprising combination of **abamectin 0.20 % w/v**, Tween 80, benzyl alcohol, propylene glycol, Na_2HPO_4, citric acid, **levamisole HCL 8 % w/v**, sodium selenate, and water (page 20, Example 1). Abamectin is dissolved in benzyl alcohol, mixed in Tween 80 and propylene glycol while levamisole is dissolved in Na_2HPO_4, citric acid and sodium selenate. Sorensen et al. teach a combination abamectin/levamisole drench composition comprising **abamectin 0.20 % w/v**, Tween 80, benzyl alcohol, propylene glycol, Na_2HPO_4, citric acid, **levamisole HCL 8 % w/v**, sodium selenate, cellulose gum CMC, and water (page 20-21, Example 2). Sorensen et al. teach a combination abamectin/levamisole drench composition comprising **abamectin 0.20 % w/v**, Tween 80, benzyl alcohol, propylene glycol, Na_2HPO_4, citric acid, **levamisole HCL 8 % w/v**, sodium selenate, carbopol 934, and water (page 21, Example 3). Sorensen et al. also teach a combination abamectin/levamisole drench composition comprising **abamectin 0.20 % w/v**, Tween 80, benzyl alcohol, propylene glycol, Na_2HPO_4, citric acid, **levamisole HCL 8 % w/v**, sodium selenate, xanthan gum, and water (page 21, Example 4).

Ascertainment of the Difference between Scope the Prior Art and the Claims (MPEP §2141.012)

Sorensen et al. do not explicitly teach the incorporation of the pyrrolidone solvent in the formulation. Although Sorensen et al. teach drench formulations as known by one of ordinary skill in the art can be topically or orally administered, Sorensen et al. are silent whether the form of administration is topical, parenteral, or oral. These deficiencies are cured by the teachings of Komer.

Komer teaches novel formulations for administration of an avermectin, based on the use of N-methylpyrrolidone or 2-pyrrolidone or mixtures thereof to dissolve the avermectin (see

abstract). Komer teaches avermectins are sufficiently soluble in N-methylpyrrolidone or 2-pyrrolidone and mixtures of the two, to permit them to be used as suitable solvents for ivermectin formulations for intramuscular injection, subcutaneous **injection, topical pour-on, stomach intubation, oral and drench administration** (column 2, lines 11-16). Furthermore, Komer teaches illustrative working examples for the different routes of administration, such as injectable, pour-on (topical) formulation, and oral formulations (see column 4, lines 30-67 and all column 5 and column 6, lines 1-31). Komer also teaches formulations including N-methylpyrrolidone, or 2-pyrrolidone and mixtures thereof, **have the advantages of providing higher concentrations of avermectin, allowing smaller dose quantities to be delivered, having improved stability and extended shelf life, increased concentrations of avermectin in the bloodstream and other extracellular fluid compartments and less pain, swelling and tissue damage at the injection site compared to currently available formulations (column 2, lines 47-55)**. N-methylpyrrolidone and 2-pyrrolidone can also be used for transdermal absorption applications such as pour-on formulations and transdermal patches (column 2, lines 55-58). Formulations including N-methylpyrrolidone and/or 2-pyrrolidone can be designed to provide therapeutic levels of avermectin over a sufficient period of time to be more effective against ectoparasites (column 2, lines 58-61).

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to an ordinary skilled artisan at the time the instant invention was made to modify the formulation of Sorensen et al. by incorporating the pyrrolidone organic solvent because Komer teaches the use of pyrrolidone solvents N-methylpyrrolidone or 2-pyrrolidone and mixtures of the two in an anthelmintic formulation. One

of ordinary skill in the art would have been motivated to incorporate the pyrrolidone solvent in the formulation of Sorensen et al. because formulations including N-methylpyrrolidone, or 2-pyrrolidone and mixtures thereof, **have the advantages of providing higher concentrations of avermectin, allowing smaller dose quantities to be delivered, having improved stability and extended shelf life, increased concentrations of avermectin in the bloodstream and other extracellular fluid compartments and less pain, swelling and tissue damage at the injection site compared to currently available formulations (column 2, lines 47-55).** The instant specification clearly describes that levamisole is soluble in aqueous solution (page 3, line 26), whereas avermectins and milbemycins are insoluble in water (page 3, lines 25-26). Therefore, the solubility problem to be solved is for the avermectin as also clearly taught by Komer that this problem is solved by the use of pyrrolidone solvents N-methylpyrrolidone, or 2-pyrrolidone and mixtures thereof. A skilled artisan would have had a reasonable expectation of success upon combination of the prior art teachings because Sorensen et al. and Komer teach similar compositions for similar purposes namely control of parasitic infections.

It would have been prima facie obvious to an ordinary skilled artisan at the time the instant invention was made to modify the formulation of Sorensen et al. by preparing it for parenteral administration, because Komer teaches formulations containing anthelmintic agents for parenteral administration. One of ordinary skilled artisan would be motivated to have such a composition for parenteral administration, because it is a conventionally known administration system. A skilled artisan would have had a reasonable expectation of success upon combination of the prior art teachings because Sorensen et al. and Komer teach similar compositions for similar purposes namely control of parasitic infections.

In light of the forgoing discussion, one of ordinary skill in the art would have concluded that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments

Applicant's arguments filed 01/28/10 have been fully considered but they are not persuasive. *Applicants argue that the reference (Sorensen et al.) does not teach or suggest the use of a pyrrolidone solvent or that a ML and levamisole are both dissolved in a single solvent, as recited claim 1, which would bring the two active agents into a single phase. In fact, the '489 publication fairly teaches that in order to achieve stable compositions comprising a ML and levamisole, the two active agents must be separated from each other in their respective solvent systems by being present in different phases.* The examiner respectfully disagrees with applicant's assertions because the examiner reminds applicants that the rejection is based on the combination teachings of Sorensen et al. and Komer not Sorensen et al. by itself. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The examiner acknowledges in the previous rejection that Sorensen et al. do not teach the use of pyrrolidone solvent in the formulation. However, this deficiency is clearly cured by the teachings of Komer. One of ordinary skill in the art would have

been motivated to incorporate the pyrrolidone solvent in the formulation of Sorensen et al. because formulations including N-methylpyrrolidone, or 2-pyrrolidone and mixtures thereof, **have the advantages of providing higher concentrations of avermectin, allowing smaller dose quantities to be delivered, having improved stability and extended shelf life, increased concentrations of avermectin in the bloodstream and other extracellular fluid compartments and less pain, swelling and tissue damage at the injection site compared to currently available formulations (column 2, lines 47-55).** The examiner notes that the compositions taught by Sorensen et al. contain an avermectin such as abamectin in the formulation. The examiner reminds applicants that the references should be considered as a whole. Sorensen et al. indeed teach stable formulations that contain ivermectin and levamisole HCL as follows on page 44 specifically formulation LB99/96C wherein a homogenous white fluid is prepared:

Table 14 - Ivermectin, Ivermectin/Levamisole and Ivermectin/Levamisole/Praziquantel

Formulations With Silicon Dioxide and Titanium Dioxide Added

Material	LB99/96A	LB99/96B	LB99/96C	LB99/72A
Soybean Oil	40.00%	40.00%	40.00%	15.00%
Teric 380	5.00%	5.00%	5.00%	5.00%
Ivermectin @ 100%	0.50%	0.50%	0.50%	0.10%
Benzyl Alcohol	5.00%	5.00%	5.00%	1.50%
Levamisole HCl @ 100%	-	-	10.00%	3.75%
Colloidal Silicon Dioxide	1.00%	1.00%	1.00%	8.00%
Praziquantel	-	-	-	1.88%
Titanium Dioxide	-	2.00%	2.00%	-
Propylene Glycol	3.00%	3.00%	3.00%	-
NaOH (to pH 3.5)	0.21%	0.22%	0.39%	0.37%
Xanthum Gum	0.50%	0.50%	0.10%	-
Citric Acid	1.00%	1.00%	1.00%	1.00%
Water to volume	To volume	To volume	To volume	To weight
Appearance	Off white fluid which separates on standing	White fluid which separates on standing	Homogeneous white fluid	Homogeneous white gel
pH	3.5	3.5	3.5	3.5
Viscosity %	1,600cps	1,800cps	3,100cps	>100,000cps

Sorensen et al. teach that

> Note that Colloidal Silicon Dioxide was added to the formulation as a substitute for the solid component (such as Albendazole, Oxfendazole and Triclabendazole) that might desirably be found in the oral formulations. Titanium Dioxide filled a similar function to such benzimidazole solids insofar as stability is concerned as well as an UV screen.

Sorensen et al. also teach that with respect to water tolerance and drenchability in formulation LB99/96C no gelling occurred. Sorensen et al. also teach that for example cattle pour-on trials reveal on page 58 the following results:

Only the test pour-on formulation containing both ivermectin and levamisole (formulation LB 99/96C) significantly reduced the faecal egg counts in treated animals. The egg count in Group E reaching zero (100% reduction) at Day 8 post treatment. This can be explained by the greater *Cooperia* worm kill in the small intestine of this treatment group. *Cooperia* is a highly prolific egg producing worm. Of these pour-ons only the ivermectin and levamisole combination (formulation LB 99/96C) was highly effective in removing adult *Cooperia* with a 95% or greater reduction in *Cooperia* worm numbers compared with untreated controls.

Sorensen et al. also teach that with respect to the physical stability of LB 99/96C

that pour-on formulations LB 99/96A and LB99/96B both appeared physically unstable with rapid separation of the formulation. This was not true of the ivermectin and levamisole formulation (LB 99/96C) which remained homogeneous. See photo Figure 17. This was an unexpected observation. In this trial the addition of levamisole hydrochloride to the test ivermectin pour-ons significantly extended the spectrum of activity of the pour-on to include C*ooperia* and also appears to contribute to the formulations physical stability.

Applicants also argue that the formulation recited in the claims requires that both the ML active agent and levamisole are dissolved in the pyrrolidone solvent and that the formulation is stable. The surprising stability of the formulation recited in claim 1 is demonstrated by Study 11 on page 15, line 20 to page 16, line 22 of the specification. In contrast, the numerous formulations shown in Studies 1-10 on pages 6-15 of the specification exhibit unsuitable degradation of abamectin, demonstrating the difficulty in combining a ML and levamisole in a composition, consistent with Examples 1-6 of the '489 publication. The '489 publication does not teach or suggest the stable formulation of claim 1, which requires that both a ML and levamisole are present in a single phase dissolved in an organic pyrrolidone solvent. On the contrary, the

'489 publication teaches away from the formulation of the invention because it describes that the ML and levamisole are incompatible and must be carried in different solvents that are not miscible to achieve a stable formulation. Based on applicants' arguments and the teachings of Sorensen et al. with respect to the formulations in examples 1-6, the formulations resulted in unstable abamectin. However, applicants have to consider the teachings of the reference as a whole and specifically consider formulation LB 99/96C. One of ordinary skill in the art would infer from the above teachings formulation LB 99/96C is expected to be chemically also stable in the absence of evidence to the contrary. Furthermore, applicant is relying upon a comparative showing to rebut prima facie case must compare his claimed invention with closest prior art In re Holladay, 584 F.2d 384, 199 USPQ 516 (CCPA 1978); Ex parte Humber, 217 USPQ 265 (Bd. App.1961). Additionally, showing unexpected results over one of two equally close prior art references will not rebut *prima facie* obviousness unless the teachings of the prior art references are sufficiently similar to each other that the testing of one showing unexpected results would provide the same information as to the other. In re Johnson, 747 F.2d 1456, 1461, 223 USPQ 1260, 1264 (Fed. Cir. 1984). The examiner takes the position that the formulation LB 99/96C has found to be stable and effective as described above. The missing element in that formulation is a pyrrolidone solvent in which the deficiency is cured by the teachings of Komer as set forth above.

Applicants further argue that the combination of the '422 patent with the teaching of the '489 publication does not teach or suggest the formulation recited in the claims. The '422 patent describes that avermectins are sufficiently soluble in N-methylpyrrolidone (NMP) and 2-pyrrolidone and that formulations comprising avermectin active agents and NMP, 2-

pyrrolidione, or mixtures thereof, may be prepared for administration by intramuscular or subcutaneous injection, topical application, or oral administration. As noted previously, the '422 patent does not teach or suggest a combination of a ML together with levamisole. The '422 patent only teaches combinations of a ML with clorsulon in a pyrrolidone solvent. Furthermore, the '422 patent does not teach or suggest formulations comprising a milbemycin active agent with a pyrrolidone solvent. Applicants also argue that the structures of clorsulon and levamisole are quite different, as shown below. As such, one of skill in the art would expect that the two active agents would have substantially different properties, including solubility and stability in organic and aqueous solvents. The description in the '422 patent that NMP or 2-pyrrolidone may be used in formulations comprising an avermectin alone or an avermectin in combination with clorsulon does not suggest that pyrrolidone solvents may be used to prepare stable formulations comprising a ML with levamisole, which is described in the '489 publication as having quite different solubility characteristics and stability requirements (see page 1, lines 2-10). The examiner respectfully disagrees with applicants' assertions because for Komer to be a proper art does not have to teach the combination of macrocyclic lactone and levamisole as this combination is clearly addressed by the teachings of Sorensen et al. (see formulation LB 99/96C). Applicants in this section of their argument also resorted to attacking the secondary reference alone. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As applicants' asserted in their arguments and also taught by Sorensen et al. the unstability problem of the formulations in

examples 1-6 arises from the unsuitability of the formulations for long term stability of the abamectin. Komer clearly fills this deficiency by teaching formulations including N-methylpyrrolidone, or 2-pyrrolidone and mixtures thereof, **have the advantages of providing higher concentrations of avermectin, allowing smaller dose quantities to be delivered, having improved stability and extended shelf life, increased concentrations of avermectin in the bloodstream and other extracellular fluid compartments and less pain, swelling and tissue damage at the injection site compared to currently available formulations (column 2, lines 47-55).** This is a strong reason why one of ordinary skill in the art would look for the teachings of Komer to fix the problems in Sorensen et al.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 2 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sorensen et al. (WO 00/74489) in view of Komer (US Patent No. 5773422), Huet et al. (US Patent No 6,426,333), and Harvey (US Patent No 6,165,987).

Applicant Claims

The claimed subject matters of instant claim 1 are set forth above. Instant claim 2 recites a stable formulation suitable for administering to animals consisting essentially of a combination

of levamisole and an avermectin or levamisole and a milbemycin dissolved in a pyrrolidone solvent and a co-solvent selected from the group consisting of glycol ethers. Instant claim 11 recites method of treating infection of cattle with Cooperia or Ostertagia by administering a formulation recited in claim 1 or 2.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of the Sorensen et al. and Komer are set forth above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Sorensen et al. and Komer lacks the teaching of formulations comprising glycol ethers as an additional solvent. This deficiency is cured by the teachings of Huet et al and Harvey. Although Sorensen et al. teach a method of treating a ruminant mammal for nematodes, trematodes and/or cestodes comprising orally administering the formulation taught above, Sorensen et al. and Komer lack the teaching of a method of treating infection of cattle with *Cooperia* or *Ostertagia* by administering a formulation recited in claim 1. This deficiency is cured by the teachings of Harvey.

Huet et al. disclose spot-on formulation for combating parasites comprising an effective amount of a 1-phenylpyrazole derivative; and/or, an effective amount of a macrocyclic lactone or antiparasitic agent; an acceptable liquid carrier vehicle; and optionally, a crystallization inhibitor (column 4, lines 39-67 and column 6, lines 1-30). Huet et al. disclose that "the liquid carrier vehicle comprises a solvent wherein the solvent is selected from the group consisting of, dipropylene glycol n-butyl ether, ethylene glycol monoethyl ether, ethylene glycol monomethyl

ether, dipropylene glycol monomethyl ether, diethylene glycol monoethyl ether, which are glycol ethers (column 6, lines 5-20).

Harvey teaches that the anthelmintic agents need to be administered as solutions by dissolving them in solvents such as glycol ethers to be bio-available; because the solid dosage forms are poorly absorbed by the animal (column 1, lines 22-25).

Harvey teaches "a veterinary composition containing an effective amount of praziquantel, an effective amount of at least one macrolide anthelmintic selected from the group comprising the avermectins and the milbemycins, and a suitable organic solvent selected from the group consisting of glycerol formal, ethyl lactate, benzyl alcohol and N-methyl-2-pyrrolidone and the like, wherein the composition is suitable for administration to warm-blooded non-human animal (see abstract). The composition may be a solution or a paste and may be administered to the recipient animal by injection, drench or as an oral paste (see abstract). A method of treating endo- and ectoparasites in non-human animals is also claimed" (see abstract and claim 13). Harvey also teaches that "target parasite species were Haemonchus, Ostertagia, Trichostrongulus, Cooperia, Nematodirus, Oesophagostomum, Chabertis and Monezia expansa" for treatment (column 10, lines 27-30). Ostertagia and Cooperia refer to two parasitic genera and that Harvey's method is suitable in the treatment of species of each genera. A species necessarily anticipates and obviates its corresponding genus.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to an ordinary skilled artisan at the time the instant invention was made to modify the formulation of Sorensen et al. by incorporating additional solvents like glycol ethers as taught by Huet et al., because Harvey teaches that the

anthelmintic agents need to be administered as solutions by dissolving them in solvents such as glycol ethers to be bio-available; because the solid dosage forms are poorly absorbed by the animal (column 1, lines 22-25). The Harvey reference is used to demonstrate the general state of the art with regard to the use of solvents such as glycol ethers in anthelmintic formulations. Furthermore, the glycol ethers are commonly known solvents in the art for providing advantages of improved stability and extended shelf life to the formulations, when compared to solid dosage forms of said anthelmintics administered to animals. A skilled artisan would have had a reasonable expectation of success upon combination of the Sorensen et al., Komer, Huet et al., and Harvey teachings because Sorensen et al., Komer, Huet et al., and Harvey teach within the same field of endeavor and address the same problem, namely the treatment of parasitic infections.

It would have been prima facie obvious to a person of ordinary skill in the art at the time the instant invention was made to modify the method of Sorensen et al., Komer, and Huet et al. via treating parasitic infections caused by the species *Cooperia* or *Ostertagia* as taught by Harvey, because both *Cooperia* or *Ostertagia* are commonly known parasitic species that infect animals that are targeted for treatment by antiparasitic formulations as also demonstrated by Harvey. A skilled artisan would have had a reasonable expectation of success upon combination of the prior art teachings because Sorensen et al., Komer, Huet et al. and Harvey address the same problem, namely the treatment of parasitic infections, which are caused by the parasitic species.

In light of the forgoing discussion, one of ordinary skill in the art would have concluded that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments

Applicant's arguments filed 01/28/10 have been fully considered but they are not persuasive. *Applicants argue that as discussed above, the '489 publication describes that ML active agents are incompatible with levamisole and fairly teaches against combination of the two active agents in a single phase solvent system because of different solubility and stability requirements. The teaching of the '333 patent that a compositions comprising a 1-phenylpyrazole and a ML may include glycol ether solvents in combination with the teachings of the '489 publication and the '422 patent does not suggest the composition recited in the claims. Further, the '333 patent does not provide any motivation to modify the teaching of the '489 publication or the '422 patent to arrive at a stable formulation consisting essentially of levamisole and an avermectin or levamisole and a milbemycin which are dissolved in a pyrrolidone solvent and a glycol ether co- solvent, as recited in claim 2. The fact that the '333 patent teaches that a 1-phenylpyrazole, which is substantially different than levamisole, may be combined with a ML in a solvent system that includes a pyrrolidone solvent and a glycol ether does not suggest the combination of a ML and levamisole in the same solvent system because the '489 publication*

clearly teaches that a ML and levamisole are not compatible and must be present in different solvents which are immiscible in order to form a stable composition. Since applicants arguments are fairly similar to the arguments addressed in the previous section of rejection, the examiner incorporates the rebuttal arguments set forth above by reference in this section as they are equally applicable for rebutting applicants' arguments here too. The examiner respectfully disagrees with applicants' assertions because for Huet et al. to be a proper art, they do not have to teach the combination of macrocyclic lactone and levamisole as this combination is clearly addressed by the teachings of Sorensen et al. (see formulation LB 99/96C). Applicants in this section of their argument also resorted to attacking the secondary reference alone. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Huet et al. is incorporated in the rejections to remedy the incorporation of glycol ethers as secondary solvent in the composition. It would have been prima facie obvious to an ordinary skilled artisan at the time the instant invention was made to modify the formulation of Sorensen et al. by incorporating additional solvents like glycol ethers as taught by Huet et al., because Harvey teaches that the anthelmintic agents need to be administered as solutions by dissolving them in solvents such as glycol ethers to be bio-available; because the solid dosage forms are poorly absorbed by the animal (column 1, lines 22-25). The Harvey reference is used to demonstrate the general state of the art with regard to the use of solvents such as glycol ethers in anthelmintic formulations. Furthermore, the glycol ethers are commonly known solvents in the art for providing advantages of improved stability and

extended shelf life to the formulations, when compared to solid dosage forms of said anthelmintics administered to animals. The examiner in general addresses applicants' arguments with respect to the secondary actives in Harvey and Huet et al. as set forth above. The combination actives are taught by Sorensen et al. The examiner also takes the position that strong motivations are provided why one of ordinary skill in the art would combine the teachings of the above references. In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sorensen et al. (WO 00/74489) in view of Komer (US Patent No. 5773422) and Harvey (US Patent No 6,165,987, IDS reference).

Applicant Claims

Instant claim 11 recites method of treating infection of cattle with Cooperia or Ostertagia by administering a formulation recited in claim 1 or 2.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Sorensen et al. and Komer are set forth above.

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Although Sorensen et al. teach a method of treating a ruminant mammal for nematodes, trematodes and/or cestodes comprising orally administering the formulation taught above, Sorensen et al. and Komer lack the teaching of a method of treating infection of cattle with *Cooperia* or *Ostertagia* by administering a formulation recited in claim 1. This deficiency is cured by the teachings of Harvey.

Harvey teaches "a veterinary composition containing an effective amount of praziquantel, an effective amount of at least one macrolide anthelmintic selected from the group comprising the avermectins and the milbemycins, and a suitable organic solvent selected from the group consisting of glycerol formal, ethyl lactate, benzyl alcohol and N-methyl-2-pyrrolidone and the like, wherein the composition is suitable for administration to warm-blooded non-human animals. The composition may be a solution or a paste and may be administered to the recipient animal by injection, drench or as an oral paste. A method of treating endo- and ectoparasites in non-human animals is also claimed" (see abstract and claim 13). Harvey (US Patent No 6,165,987) also teaches that "target parasite species were Haemonchus, Ostertagia, Trichostrongulus, Cooperia, Nematodirus, Oesophagostomum, Chabertis and Monezia expansa" for treatment (column 10, lines 27-30). Ostertagia and Cooperia refer to two parasitic genera and that Harvey's method is suitable in the treatment of species of each genera. A species necessarily anticipates and obviates it corresponding genus.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to a person of ordinary skill in the art at the time the instant invention was made to modify the method of Sorensen et al. and Komer via treating parasitic infections caused by the species *Cooperia* or *Ostertagia* as taught by Harvey, because both *Cooperia* or *Ostertagia* are commonly known parasitic species that infect animals that are targeted for treatment by antiparasitic formulations as also demonstrated by Harvey. A skilled artisan would have had a reasonable expectation of success upon combination of the prior art teachings because Sorensen et al., Komer and Harvey address the same problem, namely the treatment of parasitic infections, which are caused by the parasitic species.

In light of the forgoing discussion, one of ordinary skill in the art would have concluded that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to arguments

Applicant's arguments filed 01/28/10 have been fully considered but they are not persuasive. *Applicants argue that as noted above, the combination of the '489 patent and the '422 patent do not teach or suggest the formulation recited in claim 1 because the '489 patent fairly teaches against combining a ML and levamisole in single solvent and a single phase due to stability issues. The teaching of the '987 patent does not correct the deficiency of the '489 publication and the '422 patent because it teaches a composition comprising a ML and a very*

different active agent (clorsulon), which would be expected to have properties that are very different than those of levamisole. Accordingly, the formulation recited in claim 1 is not obvious in view of the combination of the '489 publication, the '422 patent and the '987 patent. Since formulation of claim 1 is not obvious over the combination of the '489 publication, the '422 patent and the '987 patent, the method of treating cattle infected with Cooperia or Ostertagia using this composition is also not obvious in view of the three references. In addition, as noted above, although the '489 patent generally describes a method for the treatment of non-human animals with parasitic infections, the examples demonstrate that compositions comprising a ML and praziquantel are effective against Cooperia or Ostertagia in sheep, not cattle. The method of claim 11, which requires administration of the formulation of claim 1, which contains a different combination of active agents, to cattle infected with Cooperia or Ostertagia is not taught or suggested by the '987 patent alone or in combination with the '489 publication and the '422 patent. Since applicants arguments are fairly similar to the arguments addressed in the previous section of rejection, the examiner incorporates the rebuttal arguments set forth above by reference in this section as they are equally applicable for rebutting applicants' arguments here too. The examiner respectfully disagrees with applicants' assertions because Harvey clearly teaches a method of treating endo- and ectoparasites in non-human animals is also claimed" (see abstract and claim 13). Harvey also teaches that "target parasite species were Haemonchus, Ostertagia, Trichostrongulus, Cooperia, Nematodirus, Oesophagostomum, Chabertis and Monezia expansa" for treatment (column 10, lines 27-30). Ostertagia and Cooperia refer to two parasitic genera and that Harvey's method is suitable in the treatment of species of each genera. A species necessarily anticipates and obviates it corresponding genus. Even though the

exemplified embodiment is on sheep as claim indicates the method is applicable in non-human animals, which one of ordinary skill in the art can infer to include cattle. In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

Claims 1-11 are rejected. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIGABU KASSA whose telephone number is (571)270-5867. The examiner can normally be reached on 9 am-5 pm Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne P. Eyler can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Tigabu Kassa 04/21/10

/YVONNE L. EYLER/
Supervisory Patent Examiner, Art Unit 1619